Sirolimus: not so sparing in the Spare-the-Nephron trial

To the Editor: We recently reviewed the article by Weir *et al*,[1] which looks interesting, but there were a few caveats.

First, the study was underpowered in sample size. The targeted sample size was 170 patients per arm to achieve a power of 0.85 and a significance level of 0.05, but 25% of the patients in each arm withdrew from the study.

Second, although sirolimus (SRL) may potentially decrease calcineurin inhibitor (CNI) toxicity, the primary end point in the mycophenolate mofetil (MMF)/SRL arm at 24 months compared with MMF/CNI was not significantly different, neither in intention-to-treat analysis nor in per-protocol analysis. In all, 27.7% of patients randomized to MMF/SRL switched to MMF/CNI, which will emphasize the significance of analyzing data by per-protocol analysis. Consequently, the primary end point at 12 months was not even significant.

Third, the target levels of CNI were much higher than the current targets.[2] CNI-induced vasoconstriction may decrease glomerular filtration rate and signify the difference between arms.

Fourth, the authors reported 'there were fewer deaths and graft losses in the MMF/SRL arm, $P<0.03$', viz-à-viz Table 4, which showed a significant P value for death but not for graft loss.

Fifth, a significant increase in the mean 24-h urine PCR in the MMF/SRL arm at 24 months was reported. Although the difference between the mean PCRs may look trivial, the actual ranges of proteinuria are considerable (1.29–2.49 vs 0.34–0.74 g/day). This will magnify the risk of SRL-associated proteinuria and explain the significant prevalence of peripheral edema in the MMF/SRL group.

To conclude, further studies are required before we substitute MMF/CNI with the MMF/SRL regimen.

1. Weir MR, Mulgaonkar S, Chan L *et al.* Mycophenolate mofetil-based immunosuppression with sirolimus in renal transplantation: a randomized, controlled Spare-the-Nephron trial. *Kidney Int* 2011; **79**: 897–907.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* 2009; **9**(Suppl 3): S1–S157.

M Khaled Shamseddin[1] and Ankur Gupta[1]
[1]*Division of Nephrology, University of Ottawa, Ottawa, Ontario, Canada*
Correspondence: *Ankur Gupta, c/o Céline Déry, Division of Nephrology (Adult), The Ottawa Hospital, Riverside Campus, 1967 Riverside Drive, Room 511, Ottawa, Ontario, Canada K1H 7W9. E-mail: angupta@toh.on.ca*

Kidney International (2011) **79,** 1379; doi:10.1038/ki.2011.88

The Author Replies: We appreciate the opportunity to reply to the letter[1] of Drs Shamseddin and Gupta concerning our report on the Spare-the-Nephron (STN) trial.[2]

The first concern was that they felt the study was underpowered in sample size. As noted in our methods, the targeted sample size was 130 patients per arm, to achieve a power of 0.85, and a significance level of 0.05. To accommodate an approximate 25% of dropouts, the sample size of 170 patients per arm was targeted. Despite the dropouts during the course of the study, the predefined primary objective of the efficacy analysis, the treatment difference in the mean percentage change in renal function from baseline to 12 months after randomization as measured by iothalamate glomerular filtration rate, was statistically significant ($P=0.012$). The only reason to worry about power in a clinical trial is if no statistical significance exists, which would then create the possibility of a type 2 error; in which case, a larger sample size may be necessary to evaluate the possibility of statistical significance.

As for comment number 2, Table 4 summarizes the reasons of treatment failures in mutually exclusive categories in the way that patients were only counted into the category of their first event. Only five patients had switched at 12 months, and a total of only seven at the end of 24 months. However, among the 41 mycophenolate mofeti (MMF)/sirolimus (SRL) patients, who resumed calcineurin inhibitor (CNI) at some point during the study, a majority of them had withdrawn from the treatment period before resuming CNI, as only seven with 'resume CNI' as their first treatment failure event. This tells us that the majority of the switching was due to safety and would not alter the conclusion made from the protocol-defined primary efficacy analysis: intent-to-treat analysis for mean percent change in measured glomerular filtration rate from baseline to 12 months post-randomization.

Their third statement suggests that the target levels of CNI were much higher than current targets. It is important to note that in this trial, the individual transplant centers decided on CNI levels given their unique blend of patients and level of immunologic risk. Hence, our observations provide more perspective with regard to center-based approaches to provide immunosuppression for their patients.

In Table 4, the individual graft loss differences of three in the MMF/SRL and six in the MMF/CNI group was not different; however, when one looks at the composite of graft loss and death, with three events in the MMF/SRL group and 11 events in the MMF/CNI group, this was statistically significant with a P-value <0.03.

Finally, they note that there is a significant increase in the mean 24-h urine protein to creatinine ratio (from 0.2 ± 0.38 to 0.6 ± 1.89) in the MMF/SRL group at 24 months, whereas there is not much change in the MMF/CNI group, which changed from 0.2 ± 0.23 to 0.2 ± 0.54. We are not sure where they derived their ranges of proteinuria in the letter. We would agree that the longitudinal change in proteinuria in the MMF/SRL group requires more follow-up to see if it correlates with potential changes in renal function. However,